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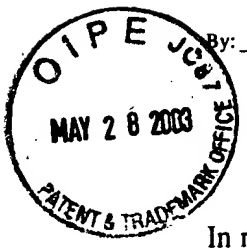
On 5-23-03

By: Linda Shaffer

PATENT

Attorney Docket No.: 016930-000921US




**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:

Richard J. Gregory, *et al.*

Application No.: 08/958,570

Filed: October 28, 1997

For: RECOMBINANT ADENOVIRAL VECTOR AND METHODS OF USE

Examiner: D. Guzo

***Declaration of Daniel C. Maneval, Under 37 C.F.R. §1.132***

Considered 7/20/03 JZ

**Box AF**
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Daniel C. Maneval, Ph.D., being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. From 1978 to 1982, I attended Boston University. I graduated in 1982 with a Bachelor of Science degree in Biomedical Engineering. I was awarded a Masters degree from the University of Southern California in 1984 in the field of Biomedical Engineering. I was awarded a Ph.D. degree from the University of Southern California in 1988 in the field Biomedical Engineering. I am currently employed by Canji, Inc. as the Director of Pharmacology. A copy of my Curriculum Vitae is attached hereto as Exhibit A.

2. I have expertise in the field of the development of treatments for human cancers. I have been continuously involved in research related to the treatment of human cancers for 16 years. In the course of my post-doctoral fellowship at St. Jude Children's Research Hospital, I was involved in the pre-clinical and clinical assessment of cancer diagnostics and therapeutics.

From 1989 to 1992, I was employed by Genentech, Inc., where I held the position of Scientist, Pharmacokinetics. I was actively involved in the pre-clinical and clinical development of the Herceptin® anti-Her2/*neu* antibody, currently approved for the treatment of breast cancer by the USFDA.

3. I have expertise in the field of the pre-clinical and early clinical development of gene therapy agents for the treatment of human cancers. Since joining Canji in 1993, I have been continuously involved with the pre-clinical and clinical development of a recombinant adenovirus encoding p53 and other recombinant adenoviruses for the treatment of cancer.

4. I am a named inventor on the above-referenced patent application. I have read and am familiar with the contents of this patent application. In addition, I have read the Office Action, dated April 18, 2002, received in the present application, and the Office Action dated April 13, 1999, referred to by the Examiner. It is my understanding that the Examiner is has alleged that claims 16-24, 26-31, 33, 35, 38 and 40 contain subject matter that is not enabled by the specification. In addition, the Examiner is concerned that claims 32, 34, 36-37, 39 and 41 are not enabled for the claimed method practiced *in vivo*.

5. It is my understanding that the present invention provides methods of obtaining expression of a tumor suppressor gene or a suicide gene in a cell by contacting the cell with an adenoviral vector that has a deletion of all or part of the protein IX coding region. The present invention also provides methods of using the vectors to treat pathologies, including cancer, in mammals.

6. In my opinion, based on the information provided in the present specification, one of skill in the art at the time would readily be able to carry out the steps necessary to administer adenoviral vectors to humans or other animals to achieve an anti-tumor effect without undue experimentation. The present specification provides ample guidance for the design and preparation of suitable vector preparations for administration, methods of administration, and dosage regimens. In particular, the specification provides a detailed description for the preparation of suitable adenoviral vectors, including suitable promoters, for the use in expressing a gene of interest, as well as methods of purification and preparation of such vectors. Particular tumor suppressor genes and suicide genes useful in the practice of the present invention are described with specificity in the specification. Given the teaching of the specification, one of

ordinary skill in the art at the time the invention was made would have been able to assemble these components into a vector using routine molecular biology methods.

7. The Examiner has cited references to support a rejection alleging that the gene therapy art was unpredictable at the time Applicants' invention such that one of skill in the art would not have been able to practice the claimed invention. The Office Action cites Anderson, "Human gene therapy", *Nature* (1998) 392:25-30 ("Anderson") and Verma and Somia, "Gene therapy - promises, problems, and prospects", *Nature* (1997) 389:239-242 ("Verma *et al.*") to support the allegation that gene therapy was an unpredictable art at the time the invention was made.

8. It is my opinion that, at the time of the invention one of skill in the art would be able to practice the full scope of the claimed invention given the teaching of the present specification. Numerous FDA approved gene therapy clinical trials involving adenoviral vectors were underway at the time the invention was made. Additionally, there were numerous reports in the scientific literature regarding the clinical administration of recombinant adenoviral vectors encoding therapeutic transgenes to human beings. Therefore, one of skill in the art would have had knowledge of these reports and, combined with the teaching of the present specification, would have been able to employ the vectors of the present invention in the treatment of human cancers without undue experimentation.

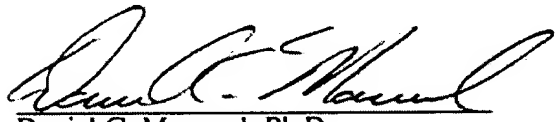
9. The experimental data provided in the instant specification demonstrates that an adenovirus vector that encodes p53 was effective in reducing the growth of established tumors and significantly enhancing survival times of tumor bearing animals. The specification also provides *in vitro* and *in vivo* results demonstrating activity of recombinant vectors which contain an anti-tumor gene. It is my belief that the specification provides data that demonstrates that the claimed methods can reduce tumor growth *in vivo*. Experiment II (pp. 32-45) describes an experiment in which the administration of an adenoviral vector encoding the p53 tumor suppressor protein was found to greatly reduce the growth of established tumors and significantly enhance survival times of tumor bearing animals. The last of the control adenovirus-treated animals died on day 83, while all five animals treated with a p53-expressing vector were still alive 130 days after tumor cell inoculation.

10. Human tumor xenograft models are generally accepted in the scientific community as reasonably predictive of the efficacy of anti-cancer agents in human beings. The present specification provides in vivo data demonstrating the efficacy of the compositions of the present invention using two human xenograft tumor models, the Hep3B and H69 mouse models. Hep3B and H69 are tumor cell lines which are used to establish tumors in animals and provide a model system for establishing therapeutic or pharmacological utility of a potential cancer treatment. Experiment II of the present specification demonstrated the efficacy of a recombinant adenoviral vector encoding p53 in the H69 human tumor xenograft model (*see*, page 40, lines 22-29 of the specification). Similarly, Experiment III at pages 45-54 and in particular page 52, lines 1-17) demonstrates that a recombinant adenoviral vector of the present invention containing the thymidine kinase gene was effective in the Hep3B human tumor xenograft model. Therefore, the specification provides data demonstrating the efficacy of the compositions of the present invention in xenograft model systems that are generally accepted as reasonably predictive of therapeutic effect in human beings. Therefore, based on the teaching of the specification, one of skill in the art would expect that the vectors of the present invention would be useful in the treatment of cancer in human beings.

11. The examiner has also alleged that the claims encompass a wide variety of tumor types and that the specification fails to provide sufficient guidance regarding the scope of the types of cancers amenable to treatment by the compositions of the present invention. It was well known in the art that mutations in tumor suppressor genes were frequently deleted in human tumor cells. In particular, defects in p53 function are associated with a broad range of tumor types and the p53 protein is central to the apoptotic pathway of human cells. Greater than 50% of all human tumors possess defects in p53 or p53 function. Therefore, the restoration of p53 function in tumor cells by delivering a gene encoding p53 via a delivery system of the present invention would be expected to be useful in suppressing a wide range of tumor types. Similarly, the expression of anti-tumor genes are effective in killing a broad range of tumor cell types. The particular example described in the specification, thymidine kinase, is an example of a anti-tumor gene which is well known in the art to have an effect on a very broad range of cell types. As such, one would expect that a broad range of cancer cells would be susceptible to killing by the expression of such anti-tumor genes. Therefore, one of skill in the art would appreciate that

the compositions of the present invention would be useful in the treatment of a broad range of human tumors.

12. Therefore, given the teaching of the specification, it is my opinion that one of skill in the art would have expected that the compositions of the present invention would have been effective in the treatment of a broad range of human tumors. Further, given the state of the art at the time the invention was made and the teaching of the specification, one of skill in the art would have been able to administer the compositions of the present invention to human beings with a reasonable expectation of anti-tumor efficacy without undue experimentation.



Daniel C. Maneval, Ph.D..

5/22/03

Date